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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	09/780,929	BREAKER ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- Th MAILING DATE of this communication app ars on the cov r sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *41-45* is/are withdrawn from consideration.

5)☒ Claim(s) *2* is/are allowed.

6)☒ Claim(s) *1,3-40 and 46-49* is/are rejected.

7)☒ Claim(s) *12-40 and 46-49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

It does not identify the city and either state or foreign country of residence of inventor Ronald Breaker. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

It does not identify the mailing or post office address of inventor Ronald Breaker. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See *37* CFR *1.63(c)* and *37* CFR *1.76.*

Response to Arguments

Applicant's election of Group 1 in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 41-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of *35 U. S. C. 112:*

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 10 are rejected under 3 5 U. S. C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instantly claimed invention is drawn to a generic ribozyme that possesses linkers that are nucleic acid aptamers, or ATP aptamers.

The specification as filed does not disclose any actual nucleic acid aptamers, or give any meaningful description as to what might comprise such aptamers that function in the context of a ribozyme. The specification provides a very general definition for a nucleic acid aptamer whereby said aptamer is any nucleic acid that interacts with any ligand, wherein said ligand may be any molecule, natural or synthetic. This definition of a ligand is so broad as to encompass anything that is not an individual atom, and therefore provides virtually no description to one of skill in the art who attempts to envision the invention as claimed. Further, while ATP aptamers are known in the art, the instant claims are drawn exclusively to aptamers that are part of the claimed ribozymes. Since it is the unique nucleotide sequence of each ribozyme that causes said

ribozyme to fold into a unique conformation, and since it is this unique conformation that confers catalytic activity to the ribozyme, the incorporation of linkers affects both catalytic and aptamer activity. Thus, to envision a functional ribozyme possessing additional aptamer capability as claimed, the ordinary artisan would require at least some structural descriptions that provide guidance as to how an aptamer could be inserted into a ribozyme such that both entities remain functional as presently claimed.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instantly claimed invention is drawn to a generic ribozyme that possesses linkers that are nucleic acid aptamers, or ATP aptamers. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use ribozymes possessing aptameric linkers as presently claimed. Additionally, a person skilled in the art would recognize that inserting a sequence with known function into another sequence with known function without eliminating either function is unpredictable. Thus, although the specification prophetically considers methodologies of inserting aptamer sequences into ribozymes such that both retain their function, such a disclosure would not be considered enabling. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention,
(C) The state of the prior art;

(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Said claims are drawn to a very broadly defined ribozyme/aptamer combination. Only six nucleotides chemically define the ribozyme, while no chemical sequence is given for an aptamer. The level of predictability in the art is such that one cannot tell by looking at a linear nucleic acid sequence whether that sequence will have catalytic activity as claimed. While there are computer programs that assist in determining the folded structure that a given sequence is likely to assume from its linear sequence, these have not been able to predict catalytic activity that may result from such folded structures. This is further complicated in the instant case by the presence of an aptamer; thus, one of ordinary skill in the art would not be able to synthesize such a ribozyme/aptamer complex with any degree of confidence that such a complex would have the properties claimed.

The specification as filed fails to provide any particular guidance that resolves the unpredictability in the art as discussed above. There is virtually no discussion of how such a ribozyme/aptamer complex is to be produced, and no examples provided that illustrate how such a functional complex might be formed. Accordingly, one skilled in the art would not accept on its face the prophetic statements of the specification that an aptamer could be inserted into the presently claimed ribozyme, given the lack of guidance in the specification and known unpredictability associated with predicting catalytic activity of folded nucleic acid sequences

from there primary (linear) structure. In view of the large number of sequences that are encompassed under the instant limitations and the very few functional ribozyme sequences that are expected to result from the claimed generic structure, and that further possess aptamer activity, one of ordinary skill in the art would have to engage in undue trial and error experimentation in order to practice the invention as claimed.

Claim Rejections - 35 USC § 101

35 U. S. C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 33-35, and 37-39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a human being, particularly in light of the generic nature of the base claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 6, 12-16, 18-23, 26-40, 46 and 47 are rejected under 35 U.S.C. 102(b) as anticipated by Sioud et al. (U.S. Patent Number 5,864,028)

The invention of the above listed claims is drawn to a generic ribozyme comprising hybridizing arms, linkers, and a catalytic core, wherein said linkers may be of defined nucleotide sequence, or said linkers are nucleotide linkers, or wherein said ribozymes possess sugar, base, or phosphate modifications, or are capped at the 3' or 5' end, or wherein said ribozyme cleaves separate RNA sequences, or possesses hybridizing arms of specified lengths, wherein said ribozymes are read as open reading frames in expression vectors comprising an initiation transcription and termination regions in expression vectors, wherein said vectors reside in cells that may be mammalian or human.

The ribozymes of the '028 patent are drawn to ribozymes comprising hybridizing arms, linkers, and a catalytic core, wherein said linkers may be of defined nucleotide sequences that match the limitations as set forth for $(N)_M$ and $(N)_N$, wherein said linkers are nucleotide linkers (e.g. SEQ ID NO 9), wherein said ribozymes possess sugar, base, or phosphate modifications, or are capped at the 3' or 5' end (e.g. col. 10, lines 45-50, and col. 19, lines 5-27), and wherein said ribozyme cleaves separate RNA sequences, or possesses hybridizing arms of specified lengths (e.g. SEQ ID NOS 1-13), wherein said ribozymes exist in expression vectors comprising an initiation transcription and termination regions, wherein said vectors reside in cells that may be mammalian or human (e.g. col 1).

Claims 1, 4, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Mandelbaum et al. (U.S. Patent Number 5,5 08,193).

The claims of the above invention are drawn to a generic ribozyme possessing linkers of specified sequences.

Mendelbaum et al. discloses a polynucleotide that meets the sequence limitations set forth in the claims listed above (e.g. SEQ ED NO. 1). Mendelbaum does not indicate whether said polynucleotide has endonuclease activity; however, the intended use or purpose of a structure as stated in the preamble (i.e. as an endonuclease) is not considered a limitation and is thus given no consideration in terms of patentability. See MPEP 2111.02.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 (a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S. C. 103 (c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 17, 19-25 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sioud et al. (U.S. Patent Number 5,864,028) in view of Beigelman et al. (U.S. Patent Number 5,672,511), and Haseloff et al. (U.S. Patent Number 5,641,673).

The invention of the above claims is drawn to ribozymes that possess non-nucleotide linkers, specific 2'-sugar modifications, and modified nucleotide "caps" of up to or at least 4 nucleotides. The invention is also drawn to vectors comprising the claimed ribozymes, open reading frames, and introns.

Sioud et al. teaches a ribozyme comprising phosphorothioate modifications and caps as discussed above, and also teaches said ribozymes in vectors. Sioud et al. does not teach ribozymes that comprise non-nucleotide linkers, specific sugar modifications, does not specify the length that said cap would be, or teach vectors that comprise open reading frames and introns.

Beigelman et al. teach ribozymes that comprises non-nucleotide linkers (figs. 1 and 3), specific 2'- sugar modifications (claim 10), and abasic (fig. 3) nucleotide caps of at least 3 nucleotides. Haseloff et al. teaches ribozymes that comprise introns and open reading frames.

It would have been obvious to one of ordinary skill in the art to take the phosphorothioate modified ribozymes of Sioud et al., (e.g. col. 10, lines 45-50, and col. 19, lines 5-27), and modify them as taught by Beigelman et al., because Sioud et al. teaches that such modifications confer resistance to endogenous nucleases and prolong bioactivity, and because Beigelman et al. further

teaches that abasic and 2' modifications can also prolong the bioactivity of ribozyme compounds. It also would have been obvious to one of ordinary skill to modify vectors containing the presently claimed ribozymes to contain intervening sequences (introns) and open reading frames. One of ordinary skill would have been motivated to clone the present ribozymes into said vectors, because Haseloff et al. teaches that the insertion of intervening sequences (introns) will keep the ribozyme inactive until it has reached its target, and because the open reading frames may encode reporter molecules that allow for the assay of ribozyme expression. One of ordinary skill in the art would have had a reasonable expectation of success in formulating such compounds, because both Sioud et al. and Beigelman et al. teach the protocols for creating such compounds, and because such protocols are routinely performed by those of ordinary skill. Thus, in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art.

Allowable Subject Matter

Claim 2 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

J. Douglas Schultz, PhD
October 28, 2002